

*REMARKS/ARGUMENTS**The Present Invention and the Pending Claims*

Claims 1-24 are pending. Claims 1-6 and 13-18 are directed to a method for producing a mixture of 5 α -pregnane derivatives of formulae (II) and (III). Claims 7-12 and 19-24 are directed to a method for producing a mixture of (20S)-7 α ,21-dihydroxy-20-methyl-5 α -pregn-3-one of formula (VI) and (20S)-7 α ,21-dihydroxy-20-methyl-5 α -pregn-1-en-3-one of formula (VII).

Summary of the Claim Amendments

Claims 1 and 7 have been amended to recite that the metal is present in an amount of 0.8 to 2.5 times the amount necessary for reducing the carbon-carbon double bond at the 4,5-positions of the compound represented by the formula (I). This amendment is supported by the specification at, for example, page 14, lines 31, through page 15, line 5. No new matter has been added by way of these amendments.

Summary of the Office Action

The Office objects to the specification and claims 1-24.

Claims 1-24 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nakazawa et al. (U.S. Patent Application Publication 2003/0181742) in combination with Moriarty et al. (*Tetrahedron Letters*, 35(44): 8103-8106 (1994)).

Claims 1-24 have been provisionally rejected for obviousness-type double patenting as allegedly unpatentable over claims 7, 8, and 13-18 of copending U.S. Patent Application No. 10/594,164 (hereinafter “the ‘164 application”).

Reconsideration of the pending claims is hereby requested.

Discussion of the Claim and Specification Objections

The Office has objected to the specification and claims 1-24. Specifically, in both the specification and claims, the side chain hydroxyl group is referred to as being at the C21-position. The Office contends, however, that based on the IUPAC numbering system,

discussed, for example, in Moss, *Pure & Appl. Chem.*, 61(10): 1783-1822 (1989), the hydroxyl is at the C22-position.

According to Moss et al., the parent compound, pregnane, has an ethyl group as a side chain substituted at the C17-position on ring D (see page 1791, section 3S-2.4 and page 1790, Table 1, the first line). In pregnane, only the C20- and C21-carbon atoms are present, and *the C22-carbon atom is absent*. Therefore, since the specification and pending claims are directed to a pregnane derivative, the correct nomenclature is used, in which a methyl group is substituted on the C20-position and a hydroxyl group is substituted on the C21-position.

In view of the foregoing, Applicants submit that no correction of the specification and/or claims is necessary with respect to the nomenclature. Accordingly, Applicants request that the objection to the specification and claims be withdrawn.

Discussion of the Obviousness Rejection

Claims 1-24 allegedly are obvious over Nakazawa et al. in combination with Moriarty et al. According to the Office, Nakazawa et al. discloses 5 α -pregnane derivatives as intermediates in the synthesis of a squalamine. The Office contends that Nakazawa et al. discloses the compounds of formulae II, IV, and VI, and implicitly discloses the compounds of formulae III and VII. The Office further asserts that Nakazawa et al. discloses the method steps, reactants, and products of claims 1-24 but does not disclose that the 21-hydroxyl group of the compound of formulae I or V is protected. Such compounds are not disclosed because Nakazawa et al. does not disclose protecting the hydroxyl group(s) prior to a reduction step, as required by the pending claims.

Moriarty et al. allegedly discloses a hydroxyl protecting group at the C-24 position in a multi-step synthesis of squalamine (see step iv in the production of compound 4 at pages 8103-8104). Moriarty et al. also allegedly discloses that the 7-hydroxyl group remains unprotected throughout most of the synthesis. Thus, it is the Office's position that Moriarty et al. discloses protecting the 24-hydroxyl group prior to a reduction step, while leaving the 7-hydroxyl group unprotected.

According to the Office, it would have been obvious to follow the synthesis described by Nakazawa et al., but with the steps reversed (i.e., a protection step followed by reduction), as taught by Moriarty et al.

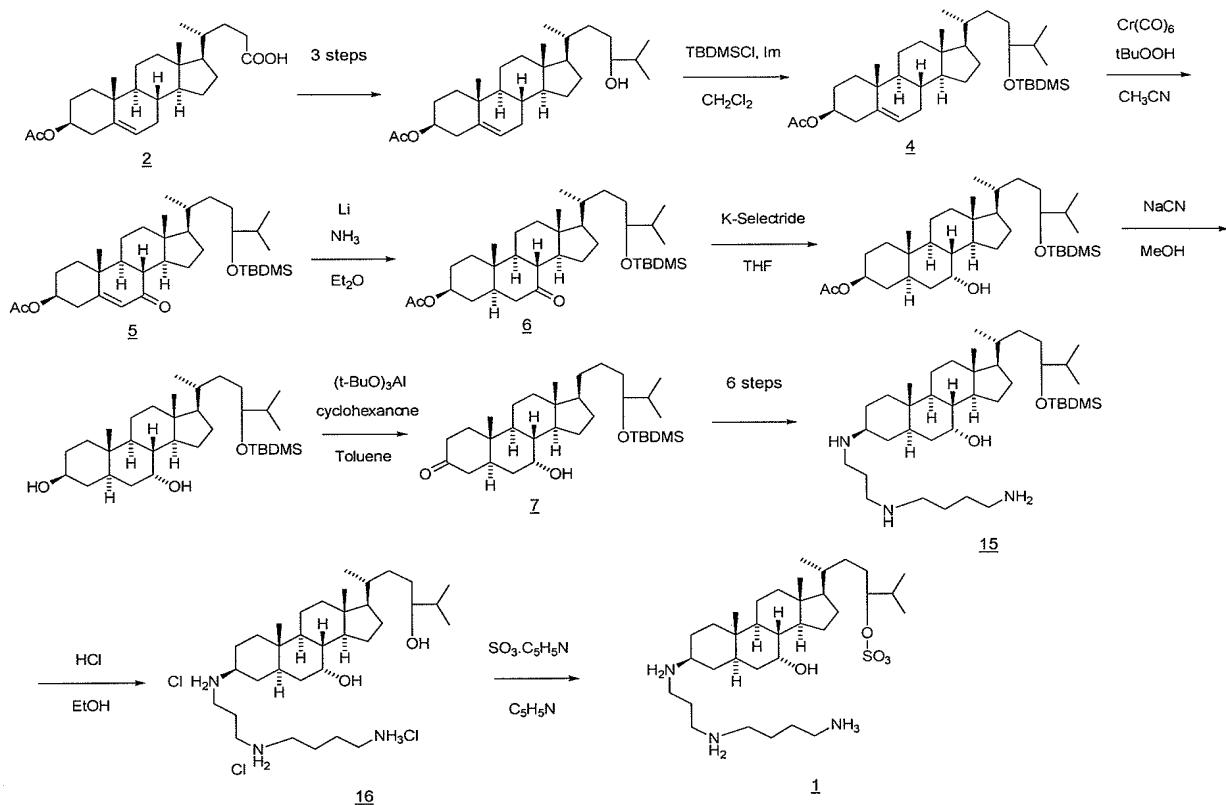
Applicants traverse this rejection based on the following discussion.

Pending claims 1-24 are directed to a method for producing *a mixture* of 5 α -pregnane derivatives (i.e., mixtures of either compounds of formulae (II) and (III) (claims 1-6 and 13-18) or formulae (VI) and (VII) (claims 7-12 and 19-24)). Applicants have discovered that the amount of the reducing reagent used in the reaction is important to obtaining *a mixture* of the ketone compound and the en-one compound.

The claimed mixture is not ultimately obtained in the reaction of Nakazawa et al. Instead, in Example 1 of Nakazawa et al., only the ketone compound (i.e., a compound of formula (II) or (VI)) is produced (paragraph 0105). Specifically, in Example 1 of Nakazawa et al., the amount (58.1 mmol) of lithium is 10 molar equivalents relative to (20S)-7 α ,21-dihydroxy-20-methyl-pregna-1,4-dien-3-one (5.81 mmol), which is 5.0 times the amount necessary for reducing the 4,5-double bond of the compound (I). Since a large excess of metal lithium was used in Nakazawa et al. (10 molar equivalents), the intermediate en-one compound (i.e., a compound of formula (III) or (VII)) would not be ultimately produced.

The Office concedes that Nakazawa et al. does not disclose protecting the hydroxyl group(s) prior to a reduction step, as required by the pending claims. To make up for this deficiency, the Office relies on the disclosure of Moriarty et al., which describes protecting a 24-hydroxyl group but not a 7-hydroxyl group.

The following schematic illustrates the chemical syntheses described in Moriarty et al., in which compound **5** is reduced via a Birch reduction with lithium in the presence of ammonia to form compound **6**. According to the Office, Moriarty et al. discloses protecting the 24-hydroxyl group on compound **5** prior to the Birch reduction, while leaving the 7-hydroxyl group unprotected. However, compound **5**, which is subjected to the Birch reduction, does not have a 7-hydroxyl group, as alleged by the Office, but rather has a 7-oxo group.



Moreover, the Office contends that it would have been obvious that the order of the two steps (i.e., Birch reduction and protection) disclosed in Nakazawa et al. can be reversed as taught by Moriarty et al. Applicants note that a Birch reduction does not necessarily require the protection of a hydroxyl group, since the reaction requires a proton donor (e.g., an alcohol, an inorganic acid, water, etc.). See the present specification at, for example, page 15, line 31, through page 16, line 3. When the hydroxyl group is not protected, the hydroxyl group itself can serve as the required proton donor.

Although Moriarty et al. discloses that compound 5, in which the 24-hydroxyl group is protected with tert-butyldimethylsilyl ethers (TBDMS), was subjected to a Birch reduction, the total synthesis described Moriarty et al. includes *steps other than a Birch reduction, which do require protection of the 24-hydroxyl group*. For example, in the total synthesis of Moriarty et al., the 24-hydroxyl group is required to be protected because

- the reduction using K-selectride (potassium tri-*sec*-butylborohydride), which is used in step vii proceeding from compound 6 to compound 7, will react vigorously with a hydroxyl group and decompose; and

- the Oppenauer oxidation using (t-Bu)₃Al and cyclohexanone, which is used in step ix proceeding from compound 6 to compound 7, can oxidize the 24-hydroxyl group.

Thus, Moriarty et al. describes (i) a Birch reduction which does not necessarily require a hydroxyl-protecting group and (ii) reactions that must include a hydroxyl-protecting group (e.g., the reduction using K-selectride, and the Oppenauer oxidation). Accordingly, Applicants maintain that the 24-hydroxyl group in Moriarty et al. has been protected because of reaction steps *other than the Birch reduction*.

Since the hydroxyl group at the 7-position in compound (I) typically only slowly reacts with a metal reducing agent due, most likely, to steric hindrance and does not, therefore, adversely influence the reaction, the 7-hydroxyl may or may not be protected. See the present specification at, for example, page 14, lines 14-17. In Moriarty et al., the 7 α -hydroxyl group appears to be unprotected for the same reason.

Consequently, in view of the foregoing, Applicants contend that Moriarty et al. does not provide a credible reason for one of ordinary skill in the art to protect a hydroxyl group (e.g., at the 21- or 24-position) prior to a Birch reduction. In the absence of any reason for one of ordinary skill in the art to alter the disclosed methods of the cited references so as to even possibly arrive at the inventive methods, the subject matter of the pending claims cannot be considered to be obvious in view of the cited references.

Even if, for the sake of argument, the Office Action recites a *prima facie* obviousness rejection based on the cited references, the unexpected properties attendant the inventive methods as defined by the pending claims rebut the *prima facie* obviousness rejection and confirm the patentability of the subject matter of the pending claims.

Amended pending claims 1-24 are directed to a method for producing a mixture of 5 α -pregnane derivatives (i.e., either compounds of formulae (II) and (III) (claims 1-6 and 13-18) or formulae (VI) and (VII) (claims 7-12 and 19-24)), which comprises, *inter alia*, reacting a pregnane derivative of formula (I) with a metal selected from alkali metals and alkaline earth metals in the presence of a proton donor and an amine and/or ammonia, in which the amount of the metal to be used is 0.8 to 2.5 times the amount necessary for

reducing the carbon-carbon double bond at the 4,5-positions of the compound represented by the formula (I).

The present inventors found that when a highly reactive primary hydroxyl group is present at the C21-position, the metal (e.g., lithium) is decomposed during the reduction step. As a result, the use of excess metal (e.g., lithium) is required. Under such conditions, since the primary hydroxyl group also acts as a proton donor during the Birch reduction, it becomes difficult to control the reaction, the 3-carbonyl group is further reduced to give a 3-hydroxyl compound as a by-product, and the overall yield decreases. Applicants further found that the reduction reaction of the 4,5-double bond proceeds significantly faster than the reduction reaction of the 1,2-double bond.

Given these difficulties, it was unexpectedly discovered by Applicants that the Birch reduction can be controlled when the 21-hydroxyl group is protected. Moreover, Applicants surprisingly found that, when the amount of the reducing agent is decreased from a conventional amount, such as the amount taught by Nakazawa et al., to 0.8-2.5 times the amount necessary for reducing the 4,5-double bond, the side reaction can be suppressed, and the total yield of the mixture can be increased (e.g., from 65% to 89%). See, e.g., Example 1 of the specification. Such unexpected results can be achieved based on the methods defined by the amended pending claims, which unexpected results serve to rebut any *prima facie* obviousness rejection based on Nakazawa et al. and Moriarty et al.

In view of the foregoing, Applicants respectfully request that the obviousness rejection over Nakazawa et al. in view of Moriarty et al. be withdrawn.

Discussion of the Obviousness-type Double Patenting Rejection

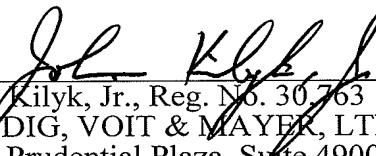
Claims 1-24 have been provisionally rejected for obviousness-type double patenting as allegedly unpatentable over certain claims of the ‘164 application. Applicants submit herewith a terminal disclaimer with respect to the ‘164 application, merely as an administrative convenience to remove the obviousness-type double patenting rejection. See *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 U.S.P.Q.2d 1392 (Fed. Cir. 1991). The terminal disclaimer is not an admission that the

subject matter of the present claims is obvious over the claims of the '164 application. In view of the foregoing, the obviousness-type double patenting rejection should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: July 15, 2009